

The Examiner contends that applicants' arguments in support of enablement are not fully persuasive in view of Baudry et al.'s disclosure that the invasive ability of *S. flexerni* is a very complex phenomenon, which involves many genes, and that it is unclear whether all these gene products are directly involved in the interaction with the cells. The Examiner further contends that the skilled artisan would be forced into undue experimentation to determine which genes or combination of genes, and which modifications can be made in order to inactivate genes.

Applicants traverse the rejection. First, claims 13-16 do not recite inactivation of genes affecting the invasive ability of *Shigella*. Therefore, the Examiner's reasons for the rejection are not relevant to claims 13-16. Accordingly, applicants respectfully submit that the rejection of claims 13-16 is in error.

Second, the mutagenesis technique taught by the specification does not require knowledge of the nucleotide sequence of the target genes or knowledge of the regions of genes responsible for biological activity. The number of nucleotides deleted or inserted is not critical to the claimed invention. The prior art discloses a wealth of information concerning the genes involved in the spread and invasion of *Shigella* and the requisite screening procedures for screening for mutations in *Shigella* genes that affect the invasion of cells, spread within infected cells, and toxin production. Genetic targets and techniques for such screening were known to the skilled artisan and, in combination with the guidance of the specification, enable the skilled artisan to make and use the claimed invention without undue experimentation. Accordingly, applicants respectfully submit that the rejection of claims 1-8, 10, and 13-23 is in error.

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Third, applicants have canceled claims 1-8, 10, and 13-23, and submitted new claims 24-46. Claims 24 and 38 do not recite inactivation of genes affecting the invasive ability of *Shigella*. In addition, claims 25-38 and 39-46 recite that an aerobactin or enterochelin gene is inactivated or do not recite inactivation of genes affecting the invasive ability of *Shigella*. Therefore, the Examiner's reasons for the rejection are not relevant to claims 24-46. Accordingly, applicants submit that new claims 24-46 obviate the rejection.

Claims 13 and 14 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner alleges that applicants' arguments are not fully persuasive in view of the claim language of claim 13, which recites "wherein said *Shigella* is other than those designated SC501, SC504, SC505, and SC506." The Examiner contends that the specification does not provide support for claiming an entire genus of the species *Shigella* based on the preferred embodiments. Applicants traverse the rejection.

New claims 24-46 do not contain the recitation "wherein said *Shigella* is other than those designated SC501, SC504, SC505, and SC506." Accordingly, applicants respectfully request withdrawal of the rejection.

Furthermore, applicants are not required to disclose every species encompassed by their claims. *In re Angstadt*, 537 F.2d 498, 502-503, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). As in *Angstadt*, applicants have provided numerous working examples. *See id.* Applicants submit that,

as in *Angstadt*, 35 U.S.C. § 112, first paragraph, does not require applicants to disclose every species capable of working in the claimed invention.

In addition, the Revised Interim Written Description Guidelines indicate that:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction practice (see (1)(a), above), reduction to drawings (see (1)(b), above), or by disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see (1)(c), above).

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in **possession of the necessary common attributes or features of the elements possessed by the members of the genus** in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, para. 1.

Revised Interim Written Description Guidelines, 64 FR 71427, 71436 (1999).

Furthermore, the Revised Interim Written Description Guidelines Training Materials provide a "decision tree" for analyzing whether the written description requirement of

35 U.S.C. § 112, first paragraph has been fulfilled. Revised Interim Written Description Guidelines Training Materials at 9. The Training Materials indicate that two steps are followed in the analysis of a "genus" claim:

1. Determine whether the art indicates substantial variation among the species within the genus of the claimed subject.

and

2. Is there a representative number of species implicitly or explicitly disclosed? What is a representative number of species depends on whether one of skill in the art would recognize that applicant was in **possession of the necessary common attributes or features of the elements possessed by the members of the genus** in view of the species disclosed or claimed.

Id. See also University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 U.S.P.Q. 2d 1398, 1406 (Fed. Cir. 1997) ("A description of a genus . . . may be achieved by . . . a recitation of **structural features common to the members of the genus, which features constitute a substantial portion of the genus.**").

When applicants' specification is analyzed under the above standards, applicants have fulfilled the written description requirement of 35 U.S.C. § 112, first paragraph, because applicants provided working examples that are representative of the claimed genus. Consequently, applicants had possession of the necessary common attributes or features of the elements possessed by the members of the genus.

The Examiner has not alleged that the art indicates substantial variation among species within the claimed genus. In fact, no art was cited by the Examiner in making this rejection. Furthermore, there is no reason to conclude that the species in applicants' claimed genus have substantial variation. Rather, the species in applicants' claimed genus are predictable.

Applicants cloned the entire *Shiga*-toxin operon. (Specification at 9.) Applicants described a process for modifying the coding region of *Shiga*-toxin to generate *Tox*⁻ clones. (*Id.*) Applicants similarly described modifying the coding region of *icsA*, enterochelin, and aerobactin to generate *icsA*⁻, enterochelin⁻, and aerobactin⁻ clones. (*Id.* at 21-23.) The necessary common feature of applicants' *Tox*⁻ clones is that the *Shiga*-toxin gene has been inactivated so that they are deficient in *Shiga*-toxin production. Similarly, the necessary common feature of applicants' *icsA*⁻, enterochelin⁻, and aerobactin⁻ clones is that the gene has been inactivated so that they are deficient in their respective protein production. Using applicants' method, the skilled artisan could **predictably** generate other *Tox*⁻ clones. Similarly, the skilled artisan could **predictably** generate other *icsA*⁻, enterochelin⁻, and aerobactin⁻ clones. Thus, the skill in the art would recognize that applicants were in possession of the necessary common attributes possessed by the members of the genus. In other words, applicants had possession of representative members of the claimed genus.

The skilled artisan further recognizes that there is a known correlation between inactivation of a coding region of a gene and deficiency of protein expression from that coding region. That is, there is a known correlation between **structural** perturbations and loss of

function. Due to this known correlation, the skilled artisan immediately recognizes numerous structural changes that will eliminate function. Thus, there can be no doubt that applicants' clones are representative of the genus of clones claimed by applicants. *See* Revised Interim Written Description Guidelines, 64 FR at 71436 ("The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species . . . by functional characteristics coupled with a known or disclosed correlation between function and structure."); *See also* Revised Interim Written Description Guidelines Training Materials at 9 ("The disclosed species is representative of the genus because there is a known correlation between the structure and the function of the claimed invention and one of skill in the art would recognize that applicant was in possession of the necessary common attributes possessed by the members of the genus."). Accordingly, applicants respectfully submit that the written description requirement of 35 U.S.C. § 112, first paragraph, has been fulfilled, and respectfully request withdrawal of the rejection.

Claims 1-8, 10, and 15-23 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of "substantially." New claims 24-45 do not contain the recitation "substantially." Accordingly, applicants respectfully request withdrawal of the rejection.

Claims 17-23 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,762,941.

Solely to expedite allowance of the pending claims, and not in acquiescence to this rejection, applicants submit herewith Terminal Disclaimers in compliance with 37 C.F.R. § 1.321(b) from the assignees.

Applicants respectfully submit that this application is in condition for allowance and request the issuance of a Notice of Allowance. If the Examiner should disagree, he is invited to contact the undersigned to discuss any remaining issues.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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